Πρόγραμμα Μεταπτυχιακών Σπουδών (ΠΜΣ) «Μεθοδολογία Βιοϊατρικής Έρευνας, Βιοστατιστική και Κλινική Βιοπληροφορική»

Τμήμα Ιατρικής
Σχολή Επιστημών Υγείας
Πανεπιστήμιο Θεσσαλίας

Τίτλος διπλωματικής εργασίας

Protocol for a clinical bioequivalence study for a generic product of mometasone furoate vs Nasonex nasal spray

Πρωτόκολλο κλινικής μελέτης βιοισοδυναμίας μεταξύ γενόσημου σπρεί φουροικής μομεταζόνης και του ρινικού σπρέι Nasonex.

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Σεπτεμβριος 2018

Protocol abstract

Introduction

This is a randomized clinical trial to prove bioequivalence between nasonex and a generic mometasone fuorate product in patients with seasonal allergic rhinitis.

Methods

In the study patients with SAR will undergo through a placebo period for 7 days in which clinical evaluations will be made twice daily for their nasal symptoms using the tonal nasal symptom score.

After that randomization will follow, and double blinded, administration of nasonex, generic drug and placebo will be given to patients evaluating them with the TNSS twice daily for 2 weeks.

Outcomes

The primary objective is to determine whether the generic mometasone is therapeutically equivalent to Nasonex .Secondary objectives is to assess safety of generic mometasone versus Nasonex over the study period and to compare the efficacy of the two mometasone containing products with that of placebo.

Conclusion

The aim of the study is to prove that the generic product is equivalent to the reference one, is efficient and is safe for use.

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Study title

A randomized control study to evaluate the bioequivalence of nasonex and a generic mometasone fuorate test nasal spray

Objectives

The primary objective is to determine whether the generic mometasone is therapeutically equivalent to Nasonex

Secondary objectives is to assess safety of generic mometasone versus Nasonex over the study period and to compare the efficacy of the two mometasone containing products with that of placebo.

Design and outcomes

A parallel, multi-centered, double bind, randomized clinical trial will be conducted to test the bioequivalence of nasonex and the generic mometasone fuorate nasal spray, and their efficacy.

In both equivalence and efficacy analysis the groups will be measured by TNSS ,a common allergic rhinitis rating system which uses a four-point scale with signs and symptoms ordered in severity from 0 (no symptoms) to 3 (severe symptoms)

Equivalence is going to be evaluated by calculating the mean difference of the original drug at the end of the randomization period (total 27 measures) from the baseline reflecting total nasal symptom score (rTNSS- the mean overall intensity of the individual symptoms during the previous 24 hours, measured by the patient in the evening), applying the same calculations for the test drug and see if there is a statistical significant difference between them.The test drug should have no significant statistical difference from the nasonex ($p>0.05$).

Efficacy is going to be evaluated by comparing the mean difference of rTNSS score of both treatments with placebo.

Interventions and Duration

The duration of the trial will be 3 weeks total ,the first 7 days will be the placebo run out period and after that the randomized period will start and last 2 weeks.

At the randomized periods the participants will be divided in 3 groups in a ratio of 2: 2:1 , which will correspond to nasonex ,mometasone test nasal spray and placebo respectively.

Clinical evaluations will be made twice daily (AM & PM at the same times daily, 12 hours apart) throught the placebo run out period and the 14 days of randomized treatment period.

Sample Size and Population

672 male and female patients aged 18 years and older with a diagnosis of seasoning allergic rhinitis (SAR) and a positive skin-prick test to grass or weed pollen within the previous year.

1.Study objectives

1.1.Primary endpoint

1)Therapeutic equivalence between generic mometasone nasal spray and Nasonex.

1.2Secondary endpoint

1)Compare the efficacy of 2 mometasone products with that of the placebo

2)Equivalence between T& R in instantaneous nasal symptom scores (recorded the four nasal symptoms intensities at the time of assessment by the patient ,before administration of the study medication in the morning)

3)Comparison of rTNSS score after 7days of treatment

5)Safety of test mometasone spray versus Nasonex

2.Background and rationale

2.1 Background on Condition, Disease, or Other Primary Study Focus

Allergic rhinitis (AR) is a heterogeneous respiratory disorder that despite its high prevalence and its impact on quality of life is often undiagnosed. It is characterized by one or more symptoms including sneezing, itching, nasal congestion, and rhinorrhea. Many causative agents have been linked to AR including pollens, molds, dust mites, and animal dander. Allergic rhinitis can be divided in two categories, seasonal and perennial. Seasonal allergic rhinitis (SAR) is fairly easy to identify because of the rapid and reproducible onset and offset of symptoms in association with pollen exposure.

Given the troublesome impact of SAR, successful treatment of the condition is of particular importance. In clinical practice, the commonly used anti-inflammatory agents, such as intranasal steroids (INS), leukotriene-receptor antagonists, and antihistamines, are recommended by the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines as the first-line choice for treating AR.

INS are undoubtedly effective and safe anti-inflammatory agents, which work by controlling the rate of protein synthesis through binding to a single glucocorticoid receptor.

Mometasone furoate is a synthetic corticosteroid which has been evaluated for intranasal use in the treatment of adults and children with allergic rhinitis. In several large, well-controlled clinical trials, mometasone furoate 200 micrograms administered once daily as an aqueous intranasal spray was significantly more effective than placebo in controlling the symptoms associated with moderate to severe seasonal allergic rhinitis. Mometasone furoate was as effective as twice-daily beclomethasone dipropionate and slightly more effective than once-daily oral

loratadine in the treatment of seasonal allergic rhinitis. Mometasone furoate was also as effective as twice-daily beclomethasone dipropionate or once-daily budesonide, and significantly more effective than placebo in the prophylaxis of seasonal allergic rhinitis. The overall incidence of adverse events is similar to placebo.

2.2 Study Rationale

2.2.1 Generic versus branded mometasone

2.2.1.1 Scope

During the past years an increasing number of generic corticosteroids were introduced, in numerous countries. For generic drugs the EMEA/CBG guidelines require a bioequivalence study in which the pharmacokinetic profile and the clinical efficacy of the brand formulation (i.e. mometasone) is compared to the reference generic product. Based on bioequivalence the generic product is expected to have the same clinical efficacy as the brand formulation.

2.2.1.2 Literature overview

According to the literature, Mometasone furoate is a well tolerated intranasal corticosteroid with minimal systemic activity and an onset of action of < or = 7 hours. It is effective in the prophylaxis and treatment of seasonal allergic rhinitis and the treatment of perennial allergic rhinitis in patients with moderate to severe symptoms.

Extensive experience in both clinical trials and the clinical practice setting has firmly established the efficacy and good tolerability profile of intranasal mometasone furoate in children and adults with SAR.

The test mometasone is efficacious in the treatment of SAR in adults and shows a favorable safety profile. The results indicate that the test mometasone is therapeutically equivalent to the reference mometasone.

The first generic version of mometasone furoate monohydrate (Nasonex nasal spray) has been approved by the FDA, according to the drug's manufacturer in March 22, 2016. (announced in NEJM)

3.Study design

Type/design of trial: parallel study, double blinded

Primary endpoint :Therapeutic equivalence between generic mometasone and Nasonex

Secondary endpoint :Compare the efficacy of the two mometasone products with that of the placebo, the equivalence between T& R in instantaneous TNSS scores, compare the rTNSS score after 7days of treatment (50% of the randomized period) and also to test the safety of test mometasone spray versus Nasonex.

Study population and sample size:

672 male and female patients aged 18 years old and older with a diagnosis of SAR and a positive skin-prick test to grass or weed pollen within the previous year.

Study location:
out -patient, multi-centered study

Duration of screening period and follow-up:
The screening period will be one week where the placebo drug will be administered and afterwards the randomization will occure and the follow up period is going to last for 2 weeks.

Intervention period: Clinical evaluations will be made twice daily (AM & PM at the same times daily, 12 hours apart) throught the placebo run out period and the 14 days randomized treatment period

Description of intervention and administration:
It is a parallel group study of 3 weeks duration totally.

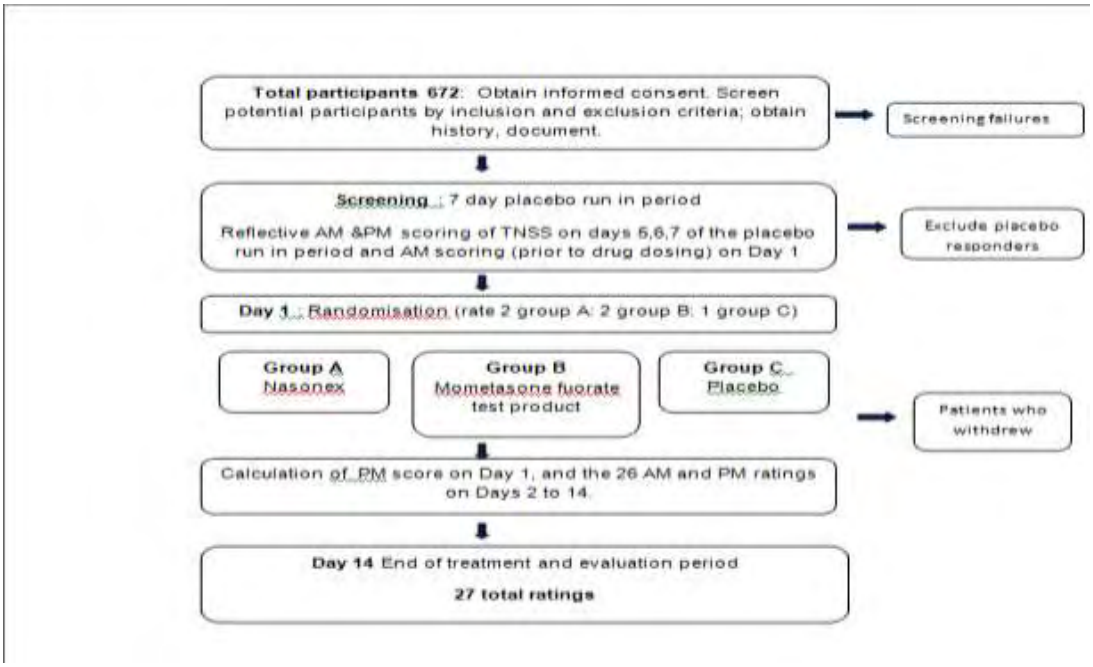
It will start with a 7 day placebo run in period to establish a baseline of mean TNSS score and to identify placebo responders

Placebo responders will be excluded from the study

After that randomization will follow, and double blinded, administration of nasonex, generic drug and placebo will be given to patients with a ratio 2:2:1 (nasonex:generic: placebo respectively)
.

Clinical evaluations will be made twice daily (AM & PM at the same times daily, 12 hours apart) throught the placebo run out period and the 14 days randomized treatment period

Table 1 :Study design



4.Selection and enrollement of participants

Inclusion Criteria:

1. Age: 18 years of age or older.
2. Signed informed consent form. For patients under the age of majority, the parent or legal guardian should sign the consent form and the child will be required to sign a patient "assent" form.
3. Sex: Male and/or non-pregnant, non-lactating females.

- All women of childbearing potential must have a negative serum pregnancy test performed within 21 days prior to the start of the study and must be using a medically acceptable form of birth control.
- Women will not be considered of childbearing potential if one of the following is reported and documented on the medical history:

  a)postmenopausal with spontaneous amenorrhea for at least six months and a serum FSH levels >40mIU/ml, or

  b)bilateral oophorectomy with or without a hysterectomy and an absence of bleeding for at least 6 months, or

  c)total hysterectomy and an absence of bleeding for at least 3 months.

4. History of seasonal allergic rhinitis of at least 2 years duration
5. Positive response to skin allergen testing to the relevant seasonal allergen (e.g. grass/tree/ragweed) for that sites geographical area within 14 months or at the time of study entry. Wheal size must be greater than or equal to (≥) 5 mm larger in diameter than diluent control via prick testing or greater than or equal to 7 mm larger in diameter than diluent control via intradermal testing.
6. Clinically active status (symptomatic) at both screening and baseline. The total nasal symptom score is to be greater than or equal to 6 on a 0-3 symptom scale with a score of at least 2 (moderate severity) for each of nasal congestion/stuffiness and one other nasal symptom score (rhinnorea, nasal itching, sneezing), and an overall disease rating of moderate or severe (e.g. total score of six or greater).
7. Weight: Age appropriate weight. BMI not to exceed 40 kg/m2
8. Tobacco Use: non-tobacco using for at least 3 months prior to study initiation.
9. Capable of providing informed consent or assent.
10. All subjects should be judged by the Principal Investigator or Medical Sub-Investigator as otherwise normal and healthy and free of clinically significant disease except for signs and symptoms of rhinoconjunctivitis that would interfere with the study schedule or evaluation of SAR during a pre-study medical evaluation performed within 21 days of the initial dose of study medication which will include:

    a)normal or non-clinically significant physical examination including nasal passage evaluation, including vital signs (pulse, temperature, respiration rate, blood pressure)

b)within normal limits or non-clinically significant laboratory evaluation results (unless otherwise specified) for the following tests: Serum Chemistries (Sodium,Albumin,Blood urea nitrogen (BUN), Potassium ,Uric Acid, Aspartate aminotransferase (AST),Chloride, Iron, Alanine aminotransferase (ALT),Calcium ,Total Cholesterol, Alkaline Phosphatase, Creatinine ,Glucose, Phosphate, Total Protein, Triglycerides, Total Bilirubin), Fasting or non-fasting may be performed based on clinical judgment, Hematology tests (Platelet Count, White blood cell count w/differential, Hemoglobin, Hematocrit, Red Blood Cell count), Urinalysis, Protein, pH, Specific Gravity,Appearance - Microscopic Examination (to be performed if urine dipstick is positive),normal or non-clinically significant 12-lead ECG, negative urine drug screen including amphetamine, barbiturates, benzodiazepines, cannabinoid (marijuana), methadone, cocaine, opiates, and phencyclidine unless legal prescribed or allowed by state/federal law.

Additional tests and or examinations may be performed, if judged necessary by the Principal Investigator or Medical Sub-Investigator.

Exclusion Criteria:

1. Institutionalized subjects.
2. Individuals who have a rTNSS score of 6 or greater at the start of the placebo run-in period but who on the randomization day (i.e. Study Day 8) no longer meet the requirement (i.e. score <6) prior to randomization, or who have a score less than 2 for Stuffiness/Congestion, or who have a score of less than 2 for all 3 of the remaining Nasal Symptoms will result in discontinuation of the subject from the study and the subject will not receive randomized treatment. The rTNSS score assessed on the randomization day (i.e. Study Day 8) will be an average of the scores from the preceding 7 scoring time points. Since randomization occurs on Day 8, then the average total score of the placebo run-in phase will include the rTNSS scores from Study Day 5 (AM & PM), Study Day 6(AM & PM), Study Day 7(AM & PM), and Study Day 8(AM).
3. Females who are pregnant or nursing.
4. History of alcohol and/or drug abuse within 1 year of subject randomization.
5. Medications:

   *All routinely used (e.g. daily) concomitant medications taken for any co-morbidity (i.e. hypertension, high triglycerides, diabetes, etc) will be documented. Subjects receiving concomitant medications should be on stable doses of the medications (defined as no change in the dose for at least 3 months and the dose is not anticipated to change during the study).

   *Subject is dependent on nasal, oral, or ocular decongestants, or anti-inflammatory agents; as determined by the principal investigator, or diagnosis of rhinitis medicamentosa.

   *Subjects who cannot tolerate nasal sprays.

   *Use of intranasal or systemic first generation antihistamines, leukotriene receptor antagonists (i.e. montelukast) or other nasal decongestants within 3 days of enrollment.

   *Use of intranasal cromolyn within 14 days of enrollment.

   *Use of intranasal or systemic second-generation antihistamines (e.g. fexofenadine, loratadine, desloratadine, cetirizine) within 10 days of enrollment.

*Use of any tricyclic anti-depressant within 30 days of enrollment.

*Use of any ophthalmic steroids within 14 days or nasal, inhaled, or systemic steroids within 30 days of the study start. Super or high potency topical steroids should not be used during the study. The use of low potency topical corticosteroids will be allowed (e.g. over-the-counter 1% hydrocortisone).

*Use of chronic medication that could affect the course of seasonal allergic rhinitis.

6. Diseases

   - Subjects who have had an upper respiratory tract or sinus infection requiring antibiotic therapy within thirty days days of enrollment, or who have had a viral upper respiratory tract infection within 30 days prior to the screening visit. History of recurrent sinusitis or chronic purulent postnasal drip

   - History of any significant cardiovascular, hepatic, renal, pulmonary, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, psychological, musculoskeletal disease, malignancies or other significant medical illness, which in the judgement of the principal investigator could interfere with the study or require medical treatment that would interfere with the study.

   - Clinical evidence of large nasal polyps, marked septal deviation, or any other nasal structural abnormality that may significantly interfere with nasal airflow, as determined by the principal investigator.

   -History of asthma over the previous two years that required chronic therapy with inhaled or systemic corticosteroids. Occasional acute or mild exercise induced asthma will be allowable on the condition that the treatment of the attacks is restricted to β-agonists only.

   -Recent exposure (within 30 days) or was at risk of being exposed to chicken pox or measles.

   -Previous seasonal allergic rhinitis or perennial allergic rhinitis that has proven unresponsive to steroid therapy.

   -Subjects with infectious rhinitis or atrophic rhinitis.

   -History of anaphylaxis and/or other severe local reactions(s) to skin testing, as determined by the Principal Investigator or Medical Sub-investigator.

   -Symptoms of common cold or upper respiratory infection or other acute illness at the screening or baseline visit.

   -Treatment for oral Candidiasis within 30 days of starting the study or a current oral Candidiasis infection

   -History of posterior subcapsular cataracts.

   -History of tuberculosis, or with the presence of uncontrolled glaucoma, cataracts, ocular herpes simplex, conjunctivitis or other eye infection not related to the diagnosis of seasonal allergic rhinitis.

   -Presence of untreated fungal, bacterial, or systemic viral infections within the previous 30 days.

7. Recent history of nasal septal surgery, nasal septal perforation (ulceration) or recent nasal injury that has not completely healed.
8. Any reason which, in the opinion of the Principal Investigator or Medical Sub-Investigator, would prevent the subject from safely participating in the study.

9. Travel outside the geographical region of pollen (local area) for more than 2 consecutive days or 3 days in total throughout the trial.
10. Anticipation of clinically significant symptoms due to perennial allergens (e.g. dust mite, molds, animal dander) prior to the anticipated start of the relevant seasonal allergy season. In other words anticipated flare of perennial allergy symptoms immediately prior to or during seasonal allergic rhinitis flare.
11. Previous participation in this study, or the patient is a member of the investigational study site staff or a member of the family of the investigational study site staff.
12. Not on stable dose of immunotherapy for at least 3 months prior to randomization and during trial.
13. Desensitization therapy to a seasonal allergen that is responsible for the subject's allergic rhinitis that is initiated or changed within the previous six months.
14. Subjects who have received an investigational drug within 30 days prior to the initial dose of study medication.

History of allergy/hypersensitivity to mometasone, other related products (i.e corticosteroids), or any of the inactive ingredients.

5. STUDY INTERVENTIONS

Before subjects may be entered into the study, a copy of the site's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent forms is required. All subjects must personally sign and date the consent form before enrollment.

5.1 Interventions, Administration, and Duration

All patients will be treated in an out-patient setting with placebo for 1 week and then after the exclusion of placebo responders they will be given one of the 3 products (placebo,nasonex,mometasone fuorate test nasal spray)

The drug will be administered with the usual recommended dose is two actuations (50 micrograms/actuation) in each nostril once daily (total dose 200 micrograms)

Prior to administration of the first dose, shake container well and actuate the pump 10 times (until a uniform spray is obtained).

Clinical evaluations will be made twice daily (AM & PM at the same times daily, 12 hours apart) throught the placebo run out period and the 14 days randomized treatment period.

5.2 Procedures for randomization

Randomisation codes will be assigned strictly sequentially as volunteers become eligible for randomisation. A randomisation list, with randomisation codes and treatments will be produced by Quintiles using a randomisation program online (https://www.randomizer.at)

At the randomization procedure the ratio of the 3 drugs will be 2:2:1 for nasonex,mometasone fuorate test drug and placebo respectively.

5.3 Handling of Study Interventions

Randomization will be via a central scheme with an interactive voice response system. During the randomized treatment period, the study will be double blinded. All nasal sprays will be contained within a plastic cover, being the same shape, size, and color for all three products ensuring blinding of all parties. There is going to be no difference in odor between the products.

5.4 Procedures for handling subjects incorrectly enrolled or randomized

Volunteers who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. When a volunteer does not meet the selection criteria, is randomised in error, and this is identified before dosing, the volunteer should be withdrawn from the study. A discussion should occur between the responsible ENT physician and the Investigator regarding whether a replacement should be considered. The ENT is to ensure all such decisions are appropriately documented. If a volunteer who does not meet the selection criteria has been dosed before the error is identified, the volunteer should be advised to continue assessments to ensure their safety, and the ENT should be informed of the error. The volunteer should be withdrawn from the study prior to further dosing.

5.5 Labelling

Labels will be prepared in accordance with local regulatory guidelines.The label will include the following information:

Name of sponsor (….) • Study drug(s) dosage form, route of administration, and quantity of dosage units • Study code • Order number (to identify the contents and packaging operation) • Directions for use (for oral use) • The period of use, eg, expiry date • Storage conditions • For clinical trial use only

5.6 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The label on the container specifies the appropriate storage.

Mometasone fuorate nasal sprays must not be stored above 25°C and do not freeze.

5.7 Accountability

The study drug provided for this study will be used only as directed in the study protocol. The study personnel will account for all study drugs dispensed to and returned from the volunteer. At the end of the study, study site personnel will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Destruction must not take place unless principal investigator has approved it. Certificates of delivery and destruction must be signed.

6.Study procedures

6.1 Description of Evaluations

6.1.1 Study Visit Definitions

The screening date is defined as the date the informed consent is signed.

It will start with a 7 day placebo run in period to establish a baseline and to identify placebo responders

Enrolment date is defined as the date of randomization.

Day 1 is defined as the day that the randomization begins.

A study week is defined as a calendar week.

Placebo run in period : reflective AM &PM scoring on days 5,6,7 of the placebo run in period and AM scoring (prior to drug dosing) on Day 1 of the 14 day randomized treatment period, resulting in **7** total AM and PM ratings.

Placebo responders would be identified based on the mean total nasal symptom score (TNSS) over the 7 total AM and PM ratings.

The study protocol would state the minimum qualifying reflective TNSS for enrollment at screening, and the same minimum qualifying TNSS would be met based on the mean of the 7 total AM and PM ratings prior to each patient's participation in the randomized portion of the study.

Symptom scores during the randomized treatment period would consist of the PM score on Day 1, and the 26 AM and PM ratings on Days 2 to 14, resulting in **27 total ratings**.

7. REMOVAL AND REPLACEMENT OF SUBJECTS

7.1 Removal of Subjects

Subjects have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject the most appropriate way to withdraw to ensure the subject's health.

Withdrawal of partial consent means that the subject does not wish to take the investigational product any longer but is still willing to collaborate in providing further data by continuing on study (eg, participate in all subsequent study visits or procedures). Subjects may decline to continue receiving the investigational product at any time during the study. These subjects, as well as those who have stopped

receiving the investigational product for other reasons (eg, investigator or sponsor concern) will be asked to participate in one, last visit for completion of the data.

Reasons for removal from the investigational product or study might include:

- administrative decision by the investigator

- ineligibility

- significant protocol deviation

- patient noncompliance

- adverse event

- withdrawal of consent

Should a subject (or a legally acceptable representative) request or decide to withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. If withdrawn consent is recorded as the reason for either ending investigational product or ending study an attempt should be made to determine the possible underlying reason for withdrawing consent, if applicable, and to record that as the primary reason. All information should be reported.

8. SAFETY ASSESSMENTS

8.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

8.2 Adverse Events

An adverse event is defined in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment." (ICH E6:1.2)

This definition of adverse events also includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (eg, cancer, diabetes, migraine headaches, gout) has increased in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

Interventions for pretreatment conditions (eg, elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered adverse events

Safety and tolerability assessments are going to include the recording of all AEs, vital signs, body weight, physical examination, nasal examination, and routine laboratory parameters (including 12-hour urinary-free cortisol and creatinine in a subgroup of patients). Information recorded on AEs included severity, relationship to study drug, and duration will be noted.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events.

Side effects

Epistaxis is generally self-limiting and mild in severity, and occurs at a higher incidence compared to placebo (5%) as described in the literature, but at a comparable or lower incidence when compared to the active control nasal corticosteroids studied (up to 15%) as reported in clinical studies for allergic rhinitis.

Systemic effects of nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods. These effects are much less likely to occur than with oral corticosteroids, and may include Cushing’s syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

In contrary to systematic corticosteroids, there is no evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression following prolonged treatment with mometasone fuorate Nasal Spray.

8.3 Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that

• is fatal

• is life threatening (places the subject at immediate risk of death)

• requires in-patient hospitalization or prolongation of existing hospitalization

• results in persistent or significant disability/incapacity

• is a congenital anomaly/birth defect

• other significant medical hazard

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet one of the definitions of serious (eg, emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the “other significant medical hazard” criterion for classification as a serious adverse event. Examples include allergic bronchospasm, convulsions, and blood dyscrasias

8.4 Reporting Procedures

The investigator is responsible for ensuring that all adverse events (as defined in 8.1 and 8.2) observed by the investigator or reported by subjects are collected and recorded in the subjects’ medical records. These adverse events will include the following:

The following adverse event attributes must be assigned by the investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); dates of onset and resolution; severity; assessment of relatedness to investigational product and action taken.

If applicable, the relationship of the adverse event to the investigational product will be assessed by means of the question: “Is there a reasonable possibility that the event may have been caused by the investigational product?” The investigator should respond to this question with either Yes or No.

Medically significant adverse events considered related to the investigational product by the investigator will be followed until resolved or considered stable.

It will be left to the investigator’s clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject’s removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

The expedited reporting will occur not later than 15 days after the investigator has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9. STATISTICAL CONSIDERATIONS

Calculating the sample size

The formula for calculating the sample size for a single mean at P=0.05 with power 90% is :

$$n \geq \left(\frac{s}{\Delta}\right)^2 (1.96+1.28)^2$$

Were **s** : 2.4 *(from previous studies : Kuna et al)*

a minimal clinically important difference : estimated threshold equal to 30% of the maximum total nasal symptom score. (the TNSS can range from 0 to 12 or 0 to 24 according to the study design) *(from previous studies Meltze et al 2016)*

$n=(2,4/0.3)^2 (10.5)^2$ = **672** patients will be needed for the trial

Statistical analysis

We will have **27 results** for **reflecting score** (mean for each patient) :Estimate difference from baseline

Equivalence analysis : compare the two mometasone products

The primary endpoint will be the reflective score

The statistical method that will be used is one way ANOVA test to compare the means for the 3 groups (a:placebo b:generic c:nasonex) and then post hoc to see the difference between the groups

The difference between the nasonex and generic will provide us the **equivalence.**

The test drug should have no significant difference from the nasonex ($p>0.05$).

After that we have to find he maximum tolerated variation (a minimal clinically important difference : estimated threshold) which by the literature is equal to 30% of the maximum total nasal symptom score.

In the European protocol (according to EMA) we must impose an equivalence limit (Δ), and the 95% Confidence Interval of Test-Reference should be included within the limits (-Δ, +Δ)

Consequently the equivalence limit (D) is 0.3 and the 95% Confidence Interval of Test-Reference that we will find should be included within the limits (-0.3, +0.3) in order to prove that the hypothesis of equivalence is right.

In the American protocol (according to FDA) we will make a logarithmic transform of the data (the mean difference of our results) and then we will do the ANOVA test, the 90% CI of Test/Reference should be included within the limits (80%, 125%), based on our ln-transform data in order to prove that the hypothesis of equivalence is right.
After establishing the equivalence with the same statistical method we will calculate the parameters for the secondary outcomes

The difference between each group and placebo will provide as the efficacy and it is going to be calculated by ANOVA.

The equivalence in the instantaneous score (by comparing the mean difference of the test and reference products) will be also calculated by the same way.

Compare the equivalence of the test and reference product at the 50% of time, by calculating the difference from the baseline of the scores at day 7, and then make a comparison using a t test.

For the adverse effects and safety ,for each treatment (test drug ,reference drug and placebo) the amount treatment-emergent adverse events will be measured and compared using ANOVA

10. PARTICIPANT RIGHTS AND CONFIDENTIALITY

10.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the ethics committee responsible for oversight of the study.

10.2 Informed Consent Form

The PI or delegate will:

• Ensure each volunteer is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
• Ensure each volunteer is notified that they are free to discontinue from the study at any time
• Ensure that each healthy volunteer is given the opportunity to ask questions and allowed time to consider the information provided
• Ensure each healthy volunteer provides signed and dated informed consent before conducting any procedure specifically for the study
• Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
• Ensure a copy of the signed ICF is given to the healthy volunteer
• Ensure that any incentives for healthy volunteers who participate in the study as well as any provisions for healthy volunteers harmed as a consequence of study participation are described in the ICF that is approved by an EC.

11. ETHICAL CONSIDERATIONS

All subjects participating in this study will be informed in writing and verbally about the purpose and procedures of the study by the investigator or research coordinator. All subjects will provided an informed consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the Ethical Committee. The formal consent of a subject (by signing the approved consent form) must be obtained before that subject undergoes any study procedure. The consent form must be signed and dated by both the subject and the investigator. The subject will be provided with a signed copy of the informed consent.

Subjects' confidentiality will be ensured by the investigator and will be maintained by the following procedures:

Subjects will be coded by their initials and a specific study number. This code will be used on all study forms or other documents with regard to this study.

The individual participants number is based on the year and month at entrance of the study, with the adaptation of number 1 to 30.

Documents that are needed in compliance with Federal regulations/ICH GCP guidelines e.g. signed informed consents, subjects identification list, will be kept at a secure location and in strict confidence by the investigator.

Subjects are free at all time to discontinue participating in the study, without providing any reason for discontinuation.

An independent physician is available for questions of the subjects.

Subjects will be informed about the outcome of the trial.

All data collected will be kept for 15 years after completion of the study

References

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4.EMA-Guideline on the investigation of bioequivalence

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